Detailed Action

Status of Application, Amendments, and/or Claims

Applicants' Remarks and Election, submitted 22 January 2010, have been entered and considered. Applicants elected Group I (claims 13, 60-66, 70-76, 78, 79 and 82-87), as well as the following species: 1) α2A adrenergic receptor and, 2) Gαi2 G-protein. Claims 26, 52-59, 67-69 and 81 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) and PCT rule 13.2, as being drawn to nonelected inventions or reciting only non-elected species, there being no allowable generic or linking claims. Applicant timely traversed the restriction/unity requirement in the response of 22 January 2010. Applicants' traversal is based on the Petition Decision under 37 C.F.R. §§ 1.144 and 1.181, issued 2 May 2006; Applicants argue that the current restriction requirement is inconsistent with the decision of the Petition. However, the most recent claims upon which the Restriction requirement of 24 July 2009 is based are not the same claims that were presented for Petition (compare the claims of 7/20/2001 with the current claims, noting that, for example, prior claims did not recite use of a "constitutively-active" receptor). Since independent claims 13 and 26 involve different special technical features (non-mutated G-protein versus mutated G-protein, respectively) they are considered separate inventions under PCT rules 13.1. Thus, the holding of lack of unity is deemed to be proper and is made FINAL.

Claims 13, 60-66, 70-76, 78, 79 and 82-87 are under examination in the instant application.

Withdrawn Objections

Informalities

Specification

Figures

The objection to the Brief Description of the Drawings for incorrect labels in Figure 6 is withdrawn, based on applicant's amendment of 22 March 2005.

Withdrawn Claim Rejections/Objections

Claim Objections

The objection to claims 26, 52, 70-80, 82, 83 and 85 for reciting or encompassing non-elected inventions, is *withdrawn*. Claims 26 and 52 have been withdrawn from examination in this Office action, rendering the objection *moot*. In addition, the recent Restriction requirement (24 July 2009) presented the elections of receptors and G-proteins as *species* elections, thus rendering the objection to claims 70-80, 82, 83 and 85 *moot* on these grounds as well.

The objection to claims 70, 82, 83 and 85 for depending from non-elected claims, is withdrawn, based on applicants' amendment of 14 June 2006.

Claim Rejections - 35 USC § 112, first paragraph – scope of enablement.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

The rejection of claims 26 and 52, under 35 USC 112, first paragraph, enablement, is *moot* in this Office action, since the claims are now withdrawn and thus not examined in the instant Office action.

Claim Rejections - 35 USC § 112, first paragraph – written description.

Likewise, the rejection of claims 26 and 52, under 35 USC 112, first paragraph, written description, is *moot* in this Office action, since the claims are now withdrawn.

Claim Rejections- 35 USC § 102

The following is a quotation of the appropriate paragraph of 35 U.S.C. 102 that forms the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> **(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.**

The rejection of claims 26 and 52 under 35 U.S.C. 102(b) as being anticipated by Price, et al, (1995, Mol. Cell. Biol., 15(11): 6188-6195, of record) is *moot* in this Office action, as the claims are currently withdrawn.

Maintained/New Rejections/Objections

Claim Objections - 35 USC § 112, second paragraph – antecedence.

Claims 61 and 63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 61 recites the limitation "the intracellular domain." There is insufficient antecedent basis for this limitation in the claim. Claim 63 is included in this rejection because it is ultimately dependent from the specifically-mentioned claim without resolving the indefiniteness issue belonging thereto.

Claim Rejections - 35 USC § 112, first paragraph – scope of enablement.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 13, 60-64, 66, 70-76, 78, 79, 82-87 are rejected under 35 USC 112, first paragraph, because the specification, while being enabling for a method of screening for ligands of GPCR's, using yeast cells comprising the positive mutations in Tables 1 and 2, for example, which result in functional yeast clones in which the heterologous receptor is constitutively active (such as the elected species MPY578αi2, shown in Table 3), does not enable use of any host cells comprising mutations in unspecified cell proteins, or comprising *all* heterologous G-protein

receptors or all G-protein mutations, including those not yet tested and those that would not function constitutively. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with the claims.

The instant Application does not reasonably provide enablement for use of yeast host cells comprising heterologous G-protein coupled receptors and comprising mutated host cell proteins, except for those specified in the instant Specification. As demonstrated in the instant Specification, most mutations in host cell genes *do not* have positive effects on cell growth (see, for example, the few positive results, indicated by "+", shown in Figure 11). The specification is not enabling for the full scope of the claims, wherein any mutation in a host cell gene or in a heterologous receptor would produce yeast cell mutants that would be functionally equivalent in the claimed method, and with the assurance that such functionally equivalent receptors and G-proteins can be made and tested without undue experimentation and with the assurance that they would have the properties needed for the claimed method (that of being able to interact sufficiently to generate a growth response in yeast). Nor are claims put forth in the instant Application that describe the enabled mutations in adequate detail such that they could be claimed as a genus.

The breadth of claims 13, 60-64, 66, 70-76, 78, 79, 82-87 is too large since the specification fails to provide any guidance on how to produce all encompassed host cell proteins, including all heterologous constitutively active receptors and G-protein subunits, and still retain the desired functional response of the heterologous GPCR's. Claims 13, 60-64, 66, 70-76, 78, 79, 82-87 refer to use of any gene or polypeptide that would produce the desired response,

without complete knowledge of the genes or polypeptides that would fall within this range. In other words, there is no guidance or working examples, in the instant case, as to which amino acids in the receptor or G-protein subunit are necessary to cause an increase in cell responsiveness due to agonist. Alternatively, there is no guidance regarding which deletions in the heterologous receptor or G-protein subunit are tolerated while maintaining the claimed functional characteristics of a responsive host cell. Figure 12 demonstrates that a few mutations in the G-protein subunit do indeed cause increased responsiveness, but there appears to be no generalizable guidelines that would predict which mutations will yield the desired results.

Due to the large quantity of experimentation necessary to determine how to use the encompassed host cells comprising heterologous constitutively-active G-protein coupled receptors, and to screen for activity, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to all encompassed mutations and chimeras, the complex nature of the invention, and the breadth of the claims which fail to recite **oligonucleotide SEQ ID NO's**--undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

35 USC § 112, first paragraph – Written Description.

Claims 13, 60-64, 66, 70-76, 78, 79, 82-87 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention.

Claims 13, 60-64, 66, 70-76, 78, 79, 82-87 are directed to methods of using yeast cells to screen for compounds that have agonist effects on a heterologous GPCR, as measured by a cell growth assay. Dependent claims recite use of a yeast host cell comprising a mutated endogenous protein, or mutated G-protein subunit, especially an alpha subunit.

The specification teaches oligonucleotides used to mutate or delete portions of a G-protein alpha subunit (SEQ ID NO: 42-63), only a few of which have been shown to have a positive effect in the cell-proliferation assay (Figure 12). The specification does not teach functional or structural characteristics of all encompassed heterologous receptors and G-protein subunits useful for the claimed methods. The description of one or a few polynucleotides encoding a G-protein polypeptide is not adequate written description of an entire genus of functionally equivalent polynucleotides and polypeptides.

To provide evidence of enablement of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity or protein domains that have not been adequately identified. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed G-protein subunit polypeptides, and therefore, would not know how to use them. Conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of use. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of use. The polypeptide itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the well-described mutations that produced functional yeast mutants (shown in Table 3), but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the

written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections- 35 USC § 102

The following is a quotation of the appropriate paragraph of 35 U.S.C. 102 that forms the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 13, 70 and 82-87 are rejected under 35 U.S.C. 102(b) as being anticipated by Price, et al, (1995, Mol. Cell. Biol., 15(11): 6188-6195). Price et al disclose use of modified yeast cells that have a greater response to growth pheromones. The authors inserted heterologous G-protein coupled receptors made constitutively active (see Abstract for example) and also produced mutant and chimeric G-protein subunits, including the alpha subunits, in yeast. Their experiments resulted in a functionally greater response of heterologous GPCR's (they primarily used somatostatin receptors), and a positive response in a cell-based growth assay (see the Discussion, page 6193). This reference meets all the limitations of claims 13, 70 and 82-87.

Claim 13 is rejected under 35 U.S.C. 102(b) as being anticipated by Imhof, et al (1996, Mol. Cell. Biol., 16(6): 2594-2605, of record). Imhof, et al disclose an agonist assay in yeast

cells comprising a heterologous human progesterone receptor and a mutated endogenous protein -RSP5- that results in an improved functional response of the heterologous receptor (see Figure 2). This reference meets the limitations of claim 13, since claim 13 does not require a positive effect of the mutation on cell growth.

Claims 13, 60-63, 70-76 and 82-84 are rejected under 35 U.S.C. 102(b) as being anticipated by Pausch, et al (1997 US Patent 5,691,188). Pausch et al disclose use of modified yeast cells that have a greater response to growth pheromones, in order to test ligands of G-protein coupled receptors. The inventors inserted heterologous G-protein coupled receptors made constitutively active in order to study pheromone-induced cellular activity (discussed throughout, but see column 2, lines 7-11 and 30-36) and also made mutant and chimeric G-protein coupled receptors and G-protein subunits, including G-alpha subunits, in yeast (see column 3, first paragraph). The inventors also performed experiments using cells in which the third intracellular loop of the GPCR was modified (column 12, 4th paragraph), and have suggested that the assay could be used for orphan receptors (see the newly-sequenced receptors cited in column 2, lines 50-61). G-protein chimeras are discussed at length throughout the patent, but many examples anticipate the instant claims. For example, column 3, under "Summary of Invention" describes mutations in which DNA encoding mammalian G-proteins is fused to DNA (or "portions thereof", which anticipates claim 72) encoding yeast G-proteins. The normal activity of G-proteins is described well (column 2, last paragraph), anticipating the further limitations of claim 73. In addition, the inventors describe mutations in GPA1 (column 3, line 25) thus anticipating claims 74-76. The methods described in claims 82-84 are discussed

throughout the patent; the abstract and Summary anticipate these claims. This reference meets all the limitations of claims 13, 60-63, 70-76 and 82-84.

Conclusion: Claims 13, 60-64, 66, 70-76, 78, 79, 82-87 are rejected for the reasons recited above.

Claim 65 is objected to for depending from a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Nickol, can be reached at (571) 272-0835.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

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/SLW/

16 April 2010